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COMMENTARY

Argon neuroprotection

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See related research by Loetscher *et al.*, <http://ccforum.com/content/13/6/R206>

Abstract

Certain noble gases, though inert, exhibit remarkable biological properties. Notably, xenon and argon provide neuroprotection in animal models of central nervous system injury. In the previous issue of *Critical Care*, Loetscher and colleagues provided further evidence that argon may have therapeutic properties for neuronal toxicity by demonstrating protection against both traumatic and oxygen-glucose deprivation injury of organotypic hippocampal cultures *in vitro*. Their data are of interest as argon is more abundant, and therefore cheaper, than xenon (the latter of which is currently in clinical trials for perinatal hypoxic-ischemic brain injury; TOBYXe; NCT00934700). We eagerly await *in vivo* data to complement the promising *in vitro* data hailing argon neuroprotection.

Every noble work is at first impossible.

Thomas Carlyle

The quest for a therapeutic to ameliorate ischemic and traumatic brain injury is certainly a noble ideal, but, thus far, a futile endeavor. In the previous issue of *Critical Care*, Loetscher and colleagues [1] provided further evidence that the inert, noble gases may have ameliorative properties in the setting of acute neuronal injury. Stimulated by a shared interest in the neuroprotective properties of another noble gas, xenon [2-4], they have shifted their focus to argon, a gas that is more abundant and cheaper to obtain. In their current investigation, they demonstrate that argon is neuroprotective when applied after an oxygen-glucose deprivation (OGD) or traumatic injury in organotypic hippocampal slice cultures *in vitro*. The models the authors employ are robust; the cultured

slices have intact synaptic networks, replicating the *in vivo* setting well; OGD is a well-described simulation of ischemic brain injury [3]; similarly, the trauma model replicates the clinical situation [2]. Loetscher and colleagues report a dose-responsive neuroprotective effect, with 50% argon appearing to be the optimal concentration for neuroprotection. Furthermore, argon was even neuroprotective when administered 3 hours after the injury. Although this report used only *in vitro* models, it is a foundation on which to base further studies that may further reveal argon's potential in a field largely bereft of interventions to improve neurological outcome from ischemic or traumatic brain injury.

We recently reported that argon (75%) prevented neuronal injury from OGD *in vitro* but that the protection afforded was inferior to that of xenon [3]. Xenon has been shown to be neuroprotective in multiple models and species and has now entered clinical trials for neonatal hypoxic-ischemic brain injury (TOBYXe; NCT00934700) [4,5]. If argon is also to be exploited clinically, it too must undergo rigorous examination in different animal models, species, laboratories, and clinically relevant injury settings [6]. While at this stage argon fulfills some criteria, it would be imprudent, in the absence of *in vivo* data, to hail argon as the elusive neuroprotective agent.

Why has there been a cascade of studies exploring the clinical utility of noble gases [1-5,7,8]? Helium, neon, argon, krypton and xenon, the first five noble gases in the periodic table, contain a full outer shell of electrons, precluding the formation of covalent bonds under biological conditions; thus, they are chemically inert. Due to the uncharged and non-polar nature of their chemical composition, these gases are able to easily partition into the brain and are able to fit snugly into amphiphilic binding cavities within proteins [9]. Depending on the properties of the surrounding electrons, some of the noble gases can create an instantaneous dipole in the atom from a charged binding site, thereby promoting a biological effect, including induction of anesthesia [10]. Neon and helium are thought to create an unfavorable balance between binding energies and repulsive forces and therefore do not produce anesthesia and other biological effects.

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In the case of xenon, there are several candidate molecules that may be capable of producing the cyto-protective properties, including the NMDA (*N*-methyl-D-aspartic acid) subtype of the glutamate receptor [11], the ATP-sensitive potassium channel [12], the two-pore potassium channel [13], and an as-yet-unidentified protein that is upstream of mTOR (mammalian target of rapamycin) [14]. A reduced ability to form induced dipoles with argon (due to its smaller size) may limit the number of available protein-binding sites when compared with xenon. Indeed, there are important pharmacodynamic differences between xenon and argon; in particular, xenon is an anesthetic at atmospheric pressure, argon is not [15]. Nonetheless, argon's lack of sedative properties may actually be beneficial as it allows administration to patients with acute, focal neurological injury (such as stroke), who would not necessarily benefit from sedation. A second major difference involves costs and consequent ease of administration. Xenon's cost necessitates administration through cumbersome recirculating and recycling systems; argon is substantially cheaper and thus may be feasibly administered through open circuits.

The development of the noble gases for neuroprotection seemed at first impossible. However, a decade of investigation of the effects of xenon has led to a clinical trial that may yet change clinical care of perinatal asphyxia. The findings of Loetscher and colleagues should encourage the pursuit of argon as a neuroprotective alternative/supplement to xenon. That would be a noble venture!

Abbreviation

OGD = oxygen-glucose deprivation.

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Competing interests

MM has received consultancy fees and funding from Air Products (Allentown, PA, USA) and Air Liquide Santé International (Paris, France) concerning the development of clinical applications for medical gases, including xenon. RDS has received consultancy fees from Air Liquide Santé International concerning the development of clinical applications for xenon. DM has interests for the development of clinical applications of argon.

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